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Could This Pig Save Your Life?

Pig-to-human transplants may soon save thousands of lives a year, make bundles of money for the technique's developers and raise a host of medical and ethical problems.

By SHERYL GAY STOLBERG

In an unmarked warehouse in the middle of a wheat field in central Ohio, a hulking 300-pound pig lies on her back, her legs tethered to a crude iron gurney in a bare, well-lighted room. The animal has been sedated into a light state of sleep, and the pale pink expanse of her belly rises and falls rhythmically with each breath. A young man in green hospital garb has just sliced a six-inch incision between the sow's nipples; now he pokes around her innards with latex-gloved hands.

The pig on the table is pregnant. The young man, a veterinary technician named Bruce Close, is about to remove her newly fertilized eggs. At 26, Close is an old hand at pig surgery; he has performed this operation more than 600 times in the two years he has been employed by Nextran, the Princeton, N.J., biotechnology company that runs this warehouse as a breeding center. This, however, is no ordinary pig farm. For the past decade, Nextran has been locked in a high-stakes race to build the perfect pig: an animal with human genes, whose organs can be transplanted into people. In the medical lexicon, this is known as xenotransplantation, and it has been an elusive dream of scientists for nearly 100 years.

Today, despite fears that pig-to-human transplants could unleash a deadly new virus, the dream is closer than ever to reality. In August, a long-awaited safety study conducted by Nextran's chief competitor, Imutran Ltd., of Cambridge, England, found no evidence of active infection in 160 people who had been treated with pig tissue for a variety of conditions. The findings come as the companies are laying the groundwork to begin testing transplanted organs in people. Sometime within the next few years, and possibly as soon as the end of next year, either the British or the Americans will grab the brass ring: approval from a regulatory agency, either the United States Food and Drug Administration or its equivalent in Britain, to perform the world's first animal-to-human transplant using a heart or a kidney from a genetically engineered pig.

Nobody expects cross-species transplants to be successful overnight.

But with time, xenotransplantation could solve the most pressing crisis in medicine — the organ shortage. It could also make the companies very rich. Unlike human organs, which are donated, pig organs will be sold, and in a climate in which demand far outstrips supply, the seller will name the price. By greatly expanding the donor pool, pigs could make transplants possible for tens of thousands of people who, because of the current rationing system, never even make the list, not to mention those in some Asian nations, where taking organs from the dead is culturally taboo. Imagine a therapy as revolutionary as penicillin and as lucrative as Viagra rolled into one.

In Ohio, Bruce Close is working toward that day. Moving quickly and in silence, he tears at layers of pig fat until he can feel the pig's uterus. Gently, he extracts the slippery pink-and-purple mass, palpating it until his fingers reach a cluster of 10 blood-rich pustules — the ovulation points." Each contains a single egg so recently joined with a sperm, through artificial insemination, that it has not yet divided from one cell into two. This is the optimal moment for creating "transgenic" piglets — animals that, at least in a genetic sense, look ever so slightly like people.

It is a bizarre, almost creepy sight, this big, fat pig upside down on an operating table, her head dangling backward over a bucket in case she vomits, her insides splayed out on a blue-paper surgical drape as a scientist rearranges the DNA of her unborn young. In a moment, the animal's eggs will be flushed out of the ovaries, collected in a tiny vial and smeared onto a glass slide; then a "microinjectionist" will examine them under a high-powered microscope and, with a needle finer than a strand of hair, insert a single human gene into each.

Later this afternoon, Close will return to the operating room to implant the growing embryos into a foster mother sow. In roughly 114 days, if all goes as Nextran hopes, she will deliver a litter that includes at least one transgenic

piglet. Yet if Close sees anything Frankensteinian in this, he does not admit it. "What I'm doing right now," he says, "may someday save people's lives."

Across the Atlantic Ocean, at an undisclosed location in the English countryside, Imutran is running its own transgenic pig farm. Like Nextran, which was purchased several years ago by Baxter International, one of the world's largest medical-products manufacturers, Imutran is owned by a drug-industry powerhouse, the Swiss-based Novartis Pharma AG, a company with three times the annual revenue and nearly seven times the research budget that Baxter has. While Nextran has been testing its pig hearts and kidneys in baboons, Imutran has been running tests in monkeys and baboons, and reporting longer survival times. Like Nextran, Imutran is facing mounting criticism as it moves closer to testing its organs in people.

Animal rights advocates, predictably, lament the fate of the poor pigs that will be used as spare-parts factories, a charge the companies shrug off by pointing to refrigerators stuffed with bacon and pork chops. What they cannot shrug off, however, are the very real safety concerns. The Campaign for Responsible Transplantation, a coalition of scientists and public-health professionals, has asked for a ban on cross-species transplant research. And one prominent xenotransplant expert, Dr. Fritz Bach, of Harvard University, who is a paid consultant to Novartis, has called for a national commission to study the risks.

And so the companies are proceeding quietly, insisting that there is no rush to the clinic. "I don't believe that there is a race in the sense of, 'Oh, let's be first,'" says David White, Imutran's chief scientist. Says John S. Logan, Nextran's scientific director, "What we all want to be is the first to be successful."

But there is a race, and in science, as in life, being first counts. "Clearly," says Jeffrey L. Platt, a transplant immunologist at the Mayo Clinic, in Rochester, Minn., "there is a competition between the two companies to enter the clinical arena." The first "whole organ" xenotransplant will attract intense press coverage, giving whoever conducts it free publicity, not to mention a spot in the medical history books. And if being first means earning the confidence of regulators and the public, then being first may well be tantamount to being successful.

Platt, for one, says that if xenotransplants could be made as safe and effective as human transplants, they would replace them. "Metaphorically speaking," he says, "it will be like the automobile repair industry. Nobody makes much effort to rebuild parts, because it is cheaper and better for your car to have a brand-new part."

If it sounds like science pushing itself to the edge of science fiction, it is. And like all good science-fiction stories, this one has the potential to end in disaster.

It is not easy to find "the pig farm," as Nextran obliquely calls its breeding warehouse. The building sits at the end of a long gravel road on a slight knoll in the middle of a 200-acre lot in the little farming hamlet of Albany, Ohio. There are no signs outside, which is by design. "We're not big on signs," Logan, the Nextran scientist, explains. On the rare occasion when uninvited guests drop in with nosy questions, a supervisor dismisses them with a simple, if less than completely truthful, explanation: "We breed pigs."

With a shock of auburn hair draped across his forehead, and a reddish-brown beard covering his chin, Logan, 44, looks more like a lumberjack than a microbiologist. Born in Scotland, he still speaks with a strong accent after nearly two decades in this country, and he has the impatient manner of someone who is always hurrying to catch the next train. Where White, the Imutran scientist, is a master of public relations and charm, Logan is cautious and reserved. He is confident enough never to confess to being the underdog, but not cocky enough to make any grand predictions about success. "When we get to the day when we are sitting here and it really works," he says, "that's the day pronouncements will be worthwhile. That's the day you have to drive for. And that's what keeps me going."

Outsiders are rarely allowed at the Nextran farm. The company line is that visitors are dangerous for the pigs; nobody sees the animals without showering first and donning company-issued, disinfected clothing, plus a surgical mask and gloves. But the policy, which includes a ban on photography, also suits Nextran's penchant for privacy, so as not to rile up animal rights advocates and antibiotech groups that oppose its work. The Nextran warehouse looks more like a pig dormitory than a pig farm, with animals housed in various rooms that run along dimly lighted, narrow corridors. There is no mud. The water is tested several times a week. The pigs are strict vegetarians; meat poses the risk of bovine spongiform encephalopathy, mad cow disease.

On this particular morning, as is the case two or three mornings each week, the miracle of birth has come to the Ohio farm. In the farrowing room, where expectant sows are kept, more than two dozen newborn piglets scamper about in their stalls, their skin a translucent pink, their umbilical cords still dangling from their bellies. In 24 hours, the piglets will be tagged and numbered, and a Nextran animal handler will snip off a tiny bit of their tails; the snippets will be shipped to the company's laboratory in Princeton, where their genetic makeup will be analyzed to see if they contain the crucial gene, or in certain cases two genes, that Nextran believes will trick the human immune system into accepting pig organs.

The breeding process is "horribly inefficient," Logan says. Typically, 20 pigs are born from every 100 gene-altered eggs, but only one is transgenic. The 19 less fortunate animals meet an untimely demise. So while there is something peculiarly endearing about the sight of these little pink critters, rooting for their first taste of mother's milk, Logan has no idea at this point if the animals are of any use to him. When I ask him what he sees, expecting perhaps some philosophical answer about the wonders of molecular biology, or the future health of mankind, he replies: "I see a bunch of little pigs. That's all I see."

At a time when biological tinkering has invaded every aspect of modern life, the sight of swine with human DNA should probably not seem alarming. Still, it is difficult to look at Nextran's pigs without wondering if there is an element of hubris to Logan's work, if porcine-people aren't better left to Greek mythology, or at least George Orwell, than to modern medicine. Clearly, in 1999, some pigs really are more equal than others.

Harold Vanderpool, a medical ethicist at the University of Texas Medical Branch, in Galveston, has a term for the visceral reaction these pigs evoke. "I call it 'the gag factor,'" he says. "We are thinking across a barrier that should never be crossed." And in point of fact, there may be a very good reason — the viruses — it should not be. Pigs have become the animal of choice in xenotransplant research for a variety of reasons. They are plentiful, and they breed easily. They are physiologically similar enough to humans. And pigs and people have lived side by side, in relative health and harmony, for centuries. Virologists say most disease-causing germs can be eliminated through careful selection and breeding. But over the past two years, they have focused their attention on one obscure organism that cannot be bred out, the porcine endogenous retrovirus, abbreviated in the medical literature as PERV.

Of all viruses, retroviruses are the most feared. They integrate their genetic code into the cells they infect, which means they multiply along with the cells. Retroviruses last for life. They are typically spread through blood or sexual contact, and they can lurk in the body for years, even decades, before causing any symptoms. "It's like a ghost virus, a stealth virus," says Jonathan S. Allan, a virologist at the Southwest Foundation for Biomedical Research, in San Antonio. "Once it splices itself into the host genome, it is virtually impossible to get it back out."

If this scenario sounds familiar, it's because over the past two decades, another retrovirus, H.I.V., believed to have originated in apes, has cut a devastating swath around the world. Most scientists, Allan included, do not believe that xenotransplants will unleash the next AIDS epidemic. But no one, not even the companies, argues that the transplants will be risk-free. While there is thus far no evidence that PERV makes people sick, it can infect human cells in the test tube. And some experts theorize that the virus could mutate into a deadly form, as H.I.V. did, and then spread through sexual contact, infecting untold numbers before causing any symptoms. While the recent Imutran study is a comfort, it looked at only 160 patients, who had been treated in hospitals around the world and were later tracked down by Novartis. What will happen when people are getting xenotransplants by the tens of thousands?

The danger may not be limited to PERV. In January 1997, a pig farmer in Ipoh, a Malaysian village about 200 miles north of Kuala Lampur, became ill with what appeared to be encephalitis. The following year, 258 Malaysian pig farmers became sick; 101 of them died. It took until March of this year for the Centers for Disease Control and Prevention to identify the cause: a brand-new virus named Nipah.

This is a point that Allan, who serves on a panel of scientific experts convened by the Food and Drug Administration to plan for its first xenotransplant clinical trial, has made repeatedly. For all the focus on PERV, he says, there may be other viruses, about which much less is known, that in the end will pose a greater danger to the public health. To justify any human experiment, the scientists conducting it must show that the benefits to the patient outweigh the risk. But xenotransplants defy that calculation: the patient benefits while society takes the risk. "The individual,"

Allan warns, "can sign a consent form and say, 'I'll take the risk because I'm going to die anyway.' But that person is signing a consent form for the whole population, the whole human race."

Still, there are good reasons to proceed. More than 62,000 Americans are now waiting to receive donated hearts, lungs, livers, kidneys and pancreases, according to the United Network for Organ Sharing. A new name is added to the list every 16 minutes, and every day 11 people die waiting. Increasing donations will not solve the problem; surgeons need young, healthy organs for transplants, so even if every dead person donated, there would still not be enough.

There is another reason, of course: money. In 1996, Salomon Brothers predicted that the global market for transgenic organs could reach $6 billion by the year 2010, a figure that explains why big pharmaceutical companies are involved. Novartis manufactures cyclosporine, an antirejection drug; the market for it would skyrocket if xenotransplants became common. Baxter's interest is self-preservation; it makes dialysis machines, which would be relegated to the medical junk heap if people with failing kidneys were given pig organs instead.

Hospitals and surgeons stand to gain as well. Transplants are expensive, and they make a good living for those who perform them. Three years ago, the Institute of Medicine calculated that if animal organs made it possible to offer a transplant to everyone in the United States who needed one, annual expenditures would rise to $20.3 billion, from $2.9 billion. Already, the Mayo Clinic has entered into what its director of heart and lung transplantation, Dr. Christopher McGregor, calls a "strategic alliance" with Nextran. McGregor is busy testing pig hearts in baboons, and the company has built a state-of-the-art breeding facility not far from the clinic so Mayo doctors can have a ready supply of pigs in the event that xenotransplantation takes off.

While the medical world is gearing up, so, too, is the Government. Donna E. Shalala, the Secretary of Health and Human Services, will soon appoint a special committee to advise her on medical, ethical and social issues surrounding xenotransplants. As the infrastructure grows, so does critics' frustration. The Campaign for Responsible Transplantation, the group pressing for a research ban, has lately been threatening to sue Shalala if she does not respond to its petition. "The prospect of a global health pandemic doesn't seem to be concerning anybody," warns Alix Fano, the campaign's director. "And the people that are voicing their concerns are either being silenced or ignored."

For a freckle-faced 19-year-old named Robert Pennington, the issue is of more than academic interest. Exactly two years ago today, a Nextran pig saved his life. With a fake diamond stud in his left ear, a silver bracelet encircling his wrist and a scrawny tuft of reddish-brown hair decorating his chin, Pennington, clad in a black T-shirt and blue jeans, looks more like an up-and-coming rock star than someone who has been at the brink of death. The vast scar that creeps along his chest and abdomen, in the shape of an upside-down Y, tells a different story, one that began in the fall of 1997, in Garland, Tex., a suburb of Dallas where Pennington was reared by his paternal grandparents, Charlotte and Ray.

Pennington was working at a family-owned carpet store when he came down with what he thought was the flu. Three weeks later, still feeling poorly, he looked in the mirror and saw that the whites of his blue eyes had turned yellow. He went to a local medical clinic, where a doctor asked for a urine sample. When Pennington handed the cup back, he noticed the liquid inside was a coffee-colored brown.

The clinic doctor, mystified, sent him home with orders to come back in two weeks to see a specialist. Four days later, he was admitted to Baylor University Medical Center, in Dallas, with what Dr. Marlon Levy, a transplant surgeon there, describes as "fulminate hepatic failure" — a sudden, overwhelming death of the liver. Without a transplant, Levy knew, the young man would be dead in a few days.

The liver's job is to clean toxins from the blood. When it stops working, ammonia and other poisons accumulate in the bloodstream and travel to the brain, which swells until the patient becomes comatose and dies. Within 24 hours of his arrival at Baylor, Pennington was showing signs of acute ammonia poisoning: hallucinations and aggression. At one point, nurses were forced to tie him to his bed. Charlotte Pennington, a gray-haired matronly woman with an abiding faith in God, was terrified. "We were praying for him," she says. "We told him to just rest and hold on to Jesus."

Pennington was placed at the top of the transplant list, but there were no livers available. In the back of his mind, Levy was already weighing another option: a highly experimental procedure, "extracorporeal perfusion," in which Pennington would be hooked up to a Nextran pig liver and his blood would be circulated through it. The idea was to use the pig liver outside the body as a bridge, in the hope that it would keep Pennington alive until a human liver could be found. The procedure had been approved by the F.D.A. for testing at Baylor. Pennington was the first candidate.

In the eight years he has been performing liver transplants at Baylor, Levy, a stocky man with slicked-down black hair and a boyish face, has watched more patients than he can remember die for lack of organs. Because of the liver's complex physiology, liver xenotransplants are a long way off; hearts or kidneys will probably be tested first. But the perfusion experiment offered Nextran a halfway step, a chance to see how the immune system responded when exposed to its organs. And it gave Levy a chance to help a patient. On Sept. 3, 1997, the first batch of Nextran pigs was trucked from Ohio to the Baylor campus.

On Oct. 2, Robert Pennington's condition took a turn for the worse. In a deep coma, and no longer able to eat or breathe on his own, he was placed on full life support. His grandmother remembers watching the sun go down that evening and wondering whether the boy she had reared practically from birth would be alive when it came up in the morning. That night at about 11, Levy called Charlotte Pennington, awakening her from a deep sleep for a hasty meeting in the intensive-care unit. They sat at Robert's bedside and talked about the pigs. In the blue spiral notebook in which she recorded her thoughts, Robert's frightened grandmother jotted these words: "uncharted territory. Not done at Baylor before." Levy told her she would need to make a decision by 8 the next morning.

The following morning, a 15-week-old, 118-pound pig was readied for surgery in the simple brick building that houses Baylor's animal lab; while Levy removed the animal's liver, an anesthesiologist inserted a line of plastic tubing in Robert's neck. Later, a second line of tubing was inserted into his groin, and the two-pound pig liver, covered by a surgical towel, was brought to Robert's bedside. The perfusion officially began at 4:10 P.M.; Robert's blood was pumped first through a heater and an oxygenator, then through the liver and then back into his body, at the rate of two quarts per minute.

Levy could see right away that it was working. "The liver had good color and texture," he says, "and it was taking up oxygen from the bloodstream." It was still cleaning Robert's blood six and a half hours later when a human liver was found in Houston, 250 miles away. In her scrapbook, Charlotte Pennington keeps a snapshot of "the pig that was sacrificed to save Robert," a Polaroid photograph given to her by one of Baylor's animal handlers, who had named the pig Sweetie Pie.

Three weeks later, the F.D.A. shut down the perfusion trial. A team of virologists in England, who had already reported that PERV could infect human cells in the test tube, had now documented two separate strains of the virus and discovered that the genes for both appeared in a wide variety of pigs, suggesting that it would be difficult to breed them out. "We were very concerned," says Dr. Philip Noguchi, the F.D.A. official who oversees xenotransplant research. "It was sufficiently worrisome that we felt it would be better to stop."

The "clinical hold," which applied not only to Nextran but also to a number of other companies using live pig tissue in experiments, was lifted once the companies developed tests to screen both pigs and patients for evidence of PERV. While the tests indicate that the Nextran and Imutran herds showed no evidence of active infection, Noguchi acknowledges that there are no guarantees. "We can only give assurance to the sensitivity of the assay as it currently stands," he says, lapsing into the kind of technotalk that bureaucrats use when they don't want to sound alarmist. In plain English: the virus may well be there; current tests may not be sensitive enough to detect it. Robert Pennington still undergoes regular tests for PERV infection; so far all have been negative.

When most Americans think of animal-to-human transplants, they remember the ill-fated 1984 attempt by Dr. Leonard Bailey, a Loma Linda, Calif., surgeon, to put a baboon heart in a baby the world came to know only as Fae. Baby Fae died after 20 days, but hers was only the most publicized of a long string of xenotransplant failures, starting with the earliest animal-to-human organ transplants at the beginning of the century. By 1985, the year after Baby Fae got her heart, many doctors had concluded that animals and humans were simply too dissimilar for cross-species transplants to work. In the Journal of the American Medical Association, Bailey was condemned for having succumbed to "wishful thinking."

Microbiology changed all that. While Bailey was being ridiculed in the popular press, scientists were perfecting the creation of transgenic mice for the study of cancer. By the late 1980's, companies like Nextran and Imutran were trying to figure out how to use transgenic technology for commercial gain. Pigs as organ donors seemed an obvious choice, but first the companies would have to understand the genetic underpinnings of a process known as "hyperacute rejection," in which the human immune system rejects animal organs minutes to hours after transplant. Most immunologists, including Platt, of the Mayo Clinic, believe that the human complement system, a collection of proteins that attack and destroy foreign cells, is responsible for hyperacute rejection. In the early 1990's, Platt, then at Duke University, teamed up with Logan to introduce genes to suppress these proteins. In 1995, in a study that turned the xenotransplant world on its head, they reported their results: Nextran's pig hearts survived for as long as 30 hours inside baboons. The problem of hyperacute rejection, it seemed, could be solved. In England, Imutran was proceeding on a similar track.

"There was an amazing amount of excitement in the field," White, of Imutran, says. "Before that time, people measured the survival of organs transplanted from pigs to monkeys in minutes. And then you suddenly went from minutes to days. It doesn't seem very long, but it was an absolutely major breakthrough."

White sensed early on that this was the stuff of which scientific legends are made. In 1995, he boldly predicted that human experiments would begin within two years, a prediction that generated a backlash in England and spawned a spate of ethics reviews. And though it did not come true, he is not shy about tooting his own horn. "I always like to tell my story that the first transgenic pig was born in a stable on Christmas Eve," he says, only partly tongue-in-cheek. "It's a slight stretch," he says, "because, in fact, the first litter was born on the evening of the 23d but going over into midnight, on the 24th." He also had the presence of mind to give the animal a name: Astrid.

Nextran, on the other hand, gives its pigs numbers. "They still tell that story?" Logan asks, eyebrows raised. "The day before Christmas Astrid story?" He pauses a moment, then lets out a little sigh. "Well," he says finally, "I guess a good story endures."

Today, four years after their big breakthrough in hyperacute rejection, the companies are trying to understand other forms of rejection that prevent their organs from surviving for more than a few months in baboons. Regulators will not approve human experiments until the companies can demonstrate longer survival times; Noguchi, of the F.D.A., says some experts have called for a minimum of six months. So far, Imutran has come closest; it has kept pig hearts alive in baboons for as long as 99 days, as opposed to 39 days for Nextran. The difference is a sore point between the companies. Logan says that Imutran is using antirejection drugs in such high doses that a patient could die from a weakened immune system. White says Logan is wrong. Both men, however, say one thing is clear: victory in this race will be dictated as much by progress in the laboratory as by regulatory politics and concerns about public health.

"There's an old story in science," Logan says, "about climbing a hill. The question is, Once you get to the top of the hill, is it a whole series of mountains, or just this one hill? And you don't know until you get there. We are right at that stage, close to the top of the hill."